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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,410	06/21/2002	Peter Eriksson	59760 (47137)	2145

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EXAMINER	
MCGILLEM, LAURA L	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,410	ERIKSSON ET AL.	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/15/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-22,25-29 and 31-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-22,25-29 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that claims 5, 15-16 have been amended and claims 23-24 have been canceled in the amendment filed 8/15/2006. Claims 1-6, 8-22, 25-29 and 31-33 are under examination.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Inventor Moscho has made changes to his post office address, which do not appear to be initialed. Applicant states that a new oath or declaration will be filed, however, to date no new oath or declaration has been received by the Office.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8-29 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* selective electrofusion of at least two fusion partners having cell-like membranes, does not reasonably provide

enablement for *in vivo* electrofusion of two fusion partners, or for conducting *in vitro* fertilization by selective electrofusion of an egg cell or an enucleated egg cell, and a sperm cell at any development stage, or for conducting non-human cloning. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

This rejection is being maintained for reasons of record in the previous Office Action, mailed 04/13/2006 and for reasons outlined below.

Applicants submit that the instant method is directed to highly focused electrofusion between at least two fusion partners having cell-like membranes. Applicants submit that the teaching of the specification, including the examples provided and combined with what is known in the art, provides ample support for using the method of the invention for *in vivo* electrofusion of at least two fusion partners and enables one skilled in the art to make and use the instant invention without undue experimentation. Applicants submit that the specification contemplates use of the invention in a number of *in vitro* and *in vivo* settings, and teaches the variety of biological experiments in which electrofusion has been used, including *in vivo* methods of fusion [see, e.g. Ogura A., et al., 1995, Reprod. Fertil. Dev; Van Stekelenberg-Hamers, A.E.P. et al., Mol. Reprod. Dev. 1993; Heller, R. et al., Biochim. Biophys. Acta. 1990]. Applicants submit that the specification provides numerous other examples in the background section of the specification detailing extensive list of references detailing the use of electrofusion in a variety of biological settings. Applicants submit that the

specification details the use of the method for *in vivo* fusion of cells and other fusion partners on pages 11-13 and Example 3, and provides as an example of a clinical application of the method according to the invention on page 5 and Figure 5.

Applicants further submit that electroporation is well-known in the art, and has well-described uses in a number of different methods. Applicants submit that the instant method provides improvement over bulk electrofusion techniques such as taught in Sakai et al by offering control over the fusion process. Applicants submit that the method provides a highly focused electrical field allowing the precision to fuse even a single pair of cells. Applicants submit that Sakai et al supports this argument because Sakai et al teach that a shortcoming of bulk electrofusion is a low proportion of live offspring.

Applicants submit that the specification teaches and fully enables a highly focused method of electrofusion to overcome the shortcomings taught in Orentas et al, or Mekid and Mir. In response to the allegation that the invention is unpredictable because the instant method of electrofusion "might result in uneven fusion among adjacent cells wherein one cell may fuse with many liposomes," Applicants submit that the instant invention overcomes the problems of bulk electrofusion by providing a method for electrofusion between even a single pair of cells. Applicants point out Figure 2 of the specification to show that electrofusion between a selected cell and liposome using a microelectrode is possible. Applicants submit that Figures 3 and 4 illustrate successful fusion of two fusion partners using the claimed method.

Applicants submit that the disclosure and examples provide ample guidance for use of the method for the fusion of two fusion partners having cell-like membranes. Applicants submit that the specification teaches manipulation and alignment of the fusion partners, and provides examples demonstrating methods that have been used to manipulate organelles of small dimension. Applicants submit that the specification teaches the use of a micropositioner to position the cells for fusion. Applicants submit that the specification provides ample guidance for how to obtain an electrical field by use of a low or high voltage pulse generator sufficient to result in fusion between two fusion partners. Applicants submit that the specification teaches a range and duration of voltages used in the method, as well as the voltage that should be measured at the membrane of the fusion partners, and gives examples of pulse repetition rates that are suitable for use in the claimed method. Applicants submit that the specification discloses the preferred distance to position the microelectrodes from the fusion partners in order to provide a highly focused electrical field. Applicants submit that the specification teaches the type of electrode to use and their preferred diameters. Applicants submit that Figure 5 provides an example of an *in vivo* set up. Applicants submit that Example 1 provides a detailed description of cell-cell fusion, and indicates the voltage and number of pulses used, as well as provides the type of buffer preferred for successful fusion of two fusion partners. Applicants submit that Example 2 illustrates the use of the method in cell-liposome fusion, and provides the conditions that were used for successful fusion. Applicants submit that Example 3 teaches use of single open-bore silicon capillaries set up according to Figure 1, and positioned using

micromanipulators to fuse two cells. Applicants submit that Figure 4 shows that this set-up successfully allows for electrofusion between two cells. Applicants submit that the disclosure and examples provide ample evidence for the successful fusion of two fusion partners using the method of the invention.

Applicant's arguments filed 8/15/2006 have been fully considered but they are not persuasive. The scope of the claims includes *in vivo* selective electrofusion, administration of pharmaceutically active substances and fusion partners as well as a large group of possible *in vivo* cells or tumors and is therefore very broad. Although the specification may provide numerous references in the background section of the specification that detail the use of electrofusion in a variety of biological settings to illustrate what is known in the art, the skilled artisan would not be able to tell from the disclosure of this application how to use the full scope of the claimed invention as the Applicants intend the method to be performed. Applicants submit that the specification details the use of the method for *in vivo* fusion of cells and other fusion partners on pages 11-13 and Example 3, and provides as an example of a clinical application of the method according to the invention on page 5 and Figure 5. While the specification may contemplate the use of the invention in a number of *in vitro* and *in vivo* settings, the disclosure and example provided do not sufficiently teach the skilled artisan how to practice the claimed method in accordance with the scope of the claimed invention without excessive trial and error experimentation. Figure 5 is a drawing that gives the general idea of how the invention might be used for electrofusion in the brain. It does

not provide sufficient information so that the skilled artisan would know, from the instant disclosure and this figure, how to perform electrofusion in the brain.

Applicants submit that the claimed method provides a highly focused electrical field allowing the precision to fuse even a single pair of cells and therefore overcomes the unpredictability and shortcoming of bulk electrofusion methods that often produce a low proportion of live offspring from nuclear transfer methods as taught in Sakai et al. However, the unpredictability of the claimed method of selective electrofusion is also manifested in multiple factors taught by Sakai et al, such as recognized differences in progress in these techniques among various livestock animals. Sakai et al also suggest that *in vitro* culture condition may negatively affect cloning success rates as well as the possibility of cellular trauma and damage during manipulation. Applicant has not addressed art-recognized issues of this type.

Applicants submit that the advantage of the claimed method over the art is that the method is highly focused electrofusion that overcomes the disadvantage of bulk electrofusion, obviating doubts as to the identity of the somatic cells. Although the claimed method may be disclosed as a highly focused electrofusion method, the specification and Applicants' arguments do not sufficiently address art-recognized variations as taught by Mekid and Mir in the ability of different types of cells and tissues to be successfully electrofused.

Although Applicants shows that *in vitro* electrofusion between a selected cell and liposome using a microelectrode is possible in Figures 2-3 and 4, the scope of the claimed method of *in vivo* electrofusion is so broad that it encompasses many tissue

types. These tissues would be diverse, including dense bone, brain, muscle and various organs, ranging from organs with relatively homogenous types of tissue such as liver, as well as heterogeneous tissue types, such as kidney. The specification has not provided sufficient disclosure so that the skilled artisan would know how to use this method to selectively electrofuse at least two fusion partners having cell like membranes.

As discussed in the previous Office Action, the instant specification provides some guidance for electrofusion *in vitro* regarding number, strength and duration of fusion pulse as well as a broad range of electrical field strength. However, this guidance is not sufficient so that the skilled artisan would be able to use the claimed method for *in vivo* electrofusion because of the differences between the *in vitro* and *in vivo* method of this invention including the environment around the fusion partners. The physical and biochemical *in vivo* environment around two fusion partners is likely to be very different and more complex than the relatively simpler surrounding *in vitro* environment, because the *in vivo* environment would include surrounding cells and tissues. It is very likely that such differences would require a different electrical field strength and number, strength and duration of fusion pulse in order to perform the claimed method. The specification does not provide sufficient guidance so that the skilled artisan would be able to practice the *in vivo* method from the teaching and examples of the specification without excessive trial and error experimentation. A figure of an *in vivo* electrofusion set up does not provide sufficient guidance to teach the skilled artisan how to use this method.

As *In re Gardner, Roe and Willey*, 427 F.2d 786,789 (C.C.P.A. 1970), the skilled artisan would eventually find out how to use the invention after "a great deal of work". In the case of *In re Gardner, Roe and Willey*, the invention was a compound which the inventor claimed to have antidepressant activity, but was not enabled because the inventor failed to disclose how to use the invention based on insufficient disclose of effective drug dosage. The court held that "the law requires that the disclosure in the application shall inform them how to use, not how to find out how to use for themselves".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 1 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Magae et al (Appl. Micor. Biotechol., 1986, Vol. 24, 509-511).

This rejection is being maintained for reasons of record in the previous Office Action, mailed 04/13/2006 and for reasons outlined below.

Applicants submit that the instant invention is distinguished over the Magae et al reference in using at least a single electrode to provide a highly focused electric field for the fusion of at least two fusion partners as defined by the invention. Applicants submit that the prior art objection alleged by the Examiner does not address these aspects of the instant invention. Applicants submit that Magae et al do not provide a method of selective electrofusion that comprises bringing the fusion partners into contact and applying a highly focused electric field. Applicants submit that the method of Magae et al is a bulk electrofusion, made more efficient by manipulation of the conditions and size of the cell. Applicants submit that the teaching of the Magae et al reference do not anticipate the instant methods of selective electrofusion of at least two fusion partners having cell-like membranes using a highly focused electric field.

Applicant's arguments filed 8/15/2006 have been fully considered but they are not persuasive.

Applicant's arguments appear to be based on the submission that the instant method allows controllable fusion of partners with cell-like membranes using a highly focused electric field, and the method taught by Magae et al is bulk electrofusion rather than fusion with a highly focused electric field. However, the disclosure does not provide a specific definition of the phrase "highly focused" that would exclude the method taught by Magae et al. Magae et al teach that the electrofusion of plant protoplasts occurs in a drop of protoplast solution on a cover glass and results in the fusion of 10 to 20 pairs of protoplasts. This method meets the limitation of electrofusion of at least two fusion

partners, and since the electrical pulse was provided through microelectrodes to the drop of protoplast solution, it meets the limitation of a highly focused electric field.

Claims 1-2, 8-12, 15-19 and 26-29 are rejected under 35 U.S.C. 102(e) as being anticipated by (Pui et al) U.S. Patent No. 6,093,557, filed 6/5/1998.

This rejection is being maintained for reasons of record in the previous Office Action, mailed 04/13/2006 and for reasons outlined below.

Applicants submit that the '557 patent does not teach or suggest a method that provides a highly focused electric field and allows for the selective fusion of two fusion partners. Rather, the '557 patent is drawn to a method for introducing biological material into cells that depends on establishing a spray of electrically charged, dispersed particles. Applicants submit that according to the '557 invention, the electrical charge of the dispersed particles is used to provide one or more of the dispersed particles with a velocity sufficient for the introduction of one or more substantially dispersed particles into one or more of the target cells. Applicants submit that the '557 patent thus depends on acceleration of the particles such that some particles will obtain a velocity sufficient to enable them to penetrate cells. Applicants submit that the '557 invention uses a spray established in the region of a target including one or more cells (Figure 1A description). Applicants submit that the spray of charged particles are not an electric field that is highly focused on the fusion partners. The '557 reference nowhere contains a reference to a highly focused electric field, nor does it mention selectivity of fusion between two fusion partners.

Applicant's arguments filed 8/15/2006 have been fully considered but they are not persuasive.

As discussed above, the instant disclosure does not provide a specific and limiting definition of the phrase "highly focused", and the word "selective" is not specifically defined in the disclosure. The method of Pui et al is a method that establishes a spray of substantially dispersed particles that have an electrical charge applied thereto so that one or more of the dispersed particles is introduced into one or more of the target cells (see column 3, lines 14-21, in particular). Contrary to Applicants' submission that the electrical charge of the dispersed particles is used to provide one or more of the dispersed particles with a velocity sufficient for the introduction of one or more substantially dispersed particles into one or more of the target cells, the electrospraying method taught by Pui et al is not for the purpose of impact penetration. Pui et al teach that in addition to the penetration of the cells as a result of bombardment, electrospraying techniques can be used to direct the liposome droplets over the target cells and "[A]s opposed to the penetration of cells at impact", the liposomes facilitate transfer of the material into the cell through fusion. Pui et al teach that the non-uniform electric field establishes the spray of particles from the capillary tube electrode and provides for the containment of the particles to a certain area to allow for forcible contact with the target cells. Since the specification does not define "highly focused" the confinement of the electrospray anticipates a high focus on the fusion partners. Pui et al teach that the electrospraying technique can be adjusted by altering the electrical

potential or strength of the field (see column 15, lines 1-2, in particular), which is a reference to a highly focused electrical field.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

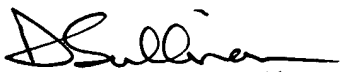
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem, PhD
10/27/2006



DANIEL M. SULLIVAN
PATENT EXAMINER